# Authors reply to the letter to the editor by Carrieri et al. HIV and alcohol - the ongoing debate

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DOI: https://doi.org/10.1097/QAI.0000000000000088

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# Reply

***To the Editors:***

We appreciate the interest from Carrieri et al and their comments regarding our article about the effect of different alcohol consumption levels on HIV surrogate markers in the Swiss HIV Cohort Study (SHCS).[1] Carrieri et al conducted a similar longitudinal analysis using data from the French ANRS APROCO-COPILOTE CO-08 cohort. In contrast to our study, they found in 1108 individuals with 11 years of follow-up that low alcohol consumption levels were associated with higher CD4 cell counts, whereas alcohol abstinence and higher levels of alcohol consumption were associated with lower CD4 counts. No significant association between alcohol consumption and virological failure was found in both cohorts.

Some important issues raised merit a few comments.

Follow-up period was indeed shorter in our study (median follow-up 2.5 years) compared with that in the French cohort (median follow-up 6.9 years). This time difference could possibly explain why in the SHCS no influence of alcohol on CD4 cell counts was observed because the toxic effect of alcohol needs time to evolve. However, despite the shorter follow-up period, we had a larger sample size (n = 2982 vs. n = 1108 in the French cohort) and our cohort also has an excellent follow-up where individuals are asked about alcohol consumption every 6 months and only very few missing data are recorded (<1%). Carrieri et al did not specify the frequency of the alcohol assessments and the level of missing data in the French cohort.

Most importantly, we would like to highlight that the 2 studies cannot be compared one to one because different baselines were used. Individuals in our study were antiretroviral therapy (ART) naive and initiated first ART. The French cohort, however, used "protease inhibitor initiating date" as baseline and only 45% were ART naive at baseline. This could cause a problem in model fitting because individuals at different stages of ART treatment have different trajectories for both HIV viral load and CD4 cell counts. In particular, the definition for virological failure used in both studies would only be appropriate in the ART initiation period. As a consequence, individuals in the French cohort were more heterogeneous with a longer period since HIV diagnosis (3.8 years vs. 1.0 years) and more AIDS events (21% vs. 13%). Furthermore, the French cohort had more injecting drug users (17% vs. 7%) and individuals coinfected with hepatitis C virus (22% vs. 10%). One could argue that individuals in the French cohort were sicker and more often at risk of severe alcohol drinking and therefore of nonadherence to ART. However, we do not have information on treatment interruption and adherence to ART in the French cohort.

Furthermore, in the French cohort, different categories for alcohol consumption were used from what we used. We applied the categories of the World Health Organization[2]: low consumption was <20 g/d for women and <40 g/d for men, moderate 20–40 g/d for women and 40–60 g/d for men, and severe >40 g/d for women and >60 g/d for men, whereas in the French study, low alcohol consumption was <10 g/d for both men and women, moderate 10–30 g/d for women and 10–40 g/d for men, and severe >30 g/d for women and >40 g/d for men, respectively. Therefore, if the French definition would be applied to our cohort, there would be fewer individuals categorized in the moderate drinking group in favor of the high drinking group. Compared with the French study, we had 46% nondrinkers (vs. 19%), 46% light health risk drinkers (vs. 54%), 5% moderate (vs. 21%), and 2% severe health risk drinkers (vs. 6%). Thus, in our cohort, there were significantly more nondrinkers and indeed fewer individuals with severe health risk drinking, limiting possibly the power in the latter category; the same was true for moderate health risk drinkers. But we would also like to rectify the comment made by Carrieri et al that we collapsed the categories of low and moderate health risk drinking, which is not the case. We fused the categories of none and light health risk drinkers, because both of them gave similar results for CD4 cell counts and HIV viral loads in the single analysis.

Besides the alcohol drinking quantity, the drinking pattern also plays an important role. Binge drinking is known to be associated with worse prognosis concerning morbidity and mortality from alcohol-induced problems and adherence to ART.[3,4] Furthermore, the type of the consumed alcohol might also be important in predicting health outcomes.[5] For the French paradox, red wine was shown to be associated with lower cardiovascular mortality, whether this is true for hard liquor as well is unknown.[6,7] As in both cohorts neither the drinking pattern nor the type of the consumed alcohol is known, no conclusions can be drawn.

The U-shaped curve between alcohol consumption levels and CD4 cell counts as shown by Carrieri et al[8] was found by the same research team for cardiovascular mortality, the so-called French paradox. According to our pathophysiological understanding and also in animal models, it is difficult to explain the U-shaped association between alcohol and CD4 cell counts. It is not clear how a postulated cytotoxic effect of alcohol can be protective for CD4 cells at a certain low level, but being toxic below and above this level.[9–11]

Overall, this French study contributes to the ongoing controversy whether alcohol has an influence on HIV surrogate markers or not. Both studies are well and carefully performed and

The authors have no conflicts of interest to disclose.

therefore justify attention in the discussion of the influence of alcohol on CD4 cell counts and HIV viral loads.

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# Plasma Lipopolysaccharide and Triglycerides are Independently Associated and Both Markers Correlate With the Development of Metabolic Syndrome in HIV Infection

***To the Editors:***

With the widespread introduction of antiretroviral therapy (ART), non-AIDS–related mortality today exceeds the AIDS-related mortality in populations with access to ART.[1] The adjusted relative risk for cardiovascular disease is reported to be around 1.5- to 2-fold compared with that of the general population.[2,3] Although classical cardiovascular risk factors such as smoking, the metabolic syndrome and its isolated components (dyslipidemia, hypertriglyceridemia, high blood pressure, central obesity, and hyperglycemia)[4] are common in HIV-infected cohorts and leading causes of cardiovascular disease in the HIV-infected population, it has been suggested that chronic immune activation and low-grade inflammation could contribute to this excess cardiovascular risk.[2] Chronic immune activation and low-grade inflammation may in turn be triggered by microbial translocation from a damaged gut.[5] With suppressive ART, we and others have reported reduced but not normalized levels of microbial translocation and chronic immune activation.[6–11] Thus, microbial translocation may be persistent in HIV-infected individuals, resulting in chronic low-grade elevation of lipopolysaccharide (LPS).

The metabolic syndrome and elevated plasma triglycerides have recently been shown to predict mortality in HIV-infected individuals.[12] In HIV seronegative populations, we have observed that LPS correlated with visceral fat and other characteristics of the metabolic syndrome, that is, dyslipidemia, obesity, blood pressure, and glycemic control.[13] In patients receiving ART, we have reported significant positive correlations between plasma LPS and triglycerides.[14] These data are in line with recent observations of strong correlation between LPS and fasting triglycerides, and an inverse relationship to high density lipoprotein (HDL) cholesterol in the general population[15] and in HIV-infected persons.[16] The aim of the present study was to investigate the putative impact of LPS and triglycerides on the development of other characteristics associated with the metabolic syndrome in HIV-infected individuals.

In an exploratory substudy of a larger longitudinal study on HIV and hypertension, 42 HIV-infected nondiabetic patients were recruited. Inclusion criteria were ART-naive status and available plasma samples at the time of nadir CD4 cell count [median age: 42; interquartile range: 32–46 years; 78% males, 80% whites, 11.9% hepatitis C antibody positive, 52.4% smokers, 29% with diagnosis of AIDS; body mass index (BMI): 22.4 (20.2–24.3) kg/m$^2$, estimated glomerular filtration rate (eGFR): 106 (95–114) mL/min, glucose 5.1 (4.7–5.4) mmol/L, cholesterol 4.6 (4.1–5.3) mmol/L, nadir CD4 cell count 240 (36–430) cells/μL and HIV RNA 44,000 (3550–165,000) copies/mL].[17,18] Plasma levels of LPS were measured at the time of nadir using the limulus amebocyte lysate assay. The samples were diluted 10-fold and then preheated to 68°C for 12 minutes to dissolve immune complexes as previously reported.[17]

Characteristics associated with the metabolic syndrome including blood pressure, glucose, triglycerides, BMI, uric acid, and HDL cholesterol were determined at follow-up 5.5 (interquartile range: 3.6–10.2) years later. At the time of follow-up, 64% of the patients

The authors have received funding from the South-Eastern Norway Regional Health Authority and Signe and Albert Bergsmarken's fund for investigation of kidney diseases.
The authors have no conflicts of interest to disclose.